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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 11/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/606,222	THOMAS ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 September 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-24,32 and 43-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-24, 32, 43-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' Amendment, filed 9/14/04, has been entered.

Claims 20, 43, 45, 47, 48-56 have been amended. Claims 20-24, 32, 43-57 are pending and under current examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 43-57 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for deleting a marker sequence from a DNA sequence that has been introduced into an mouse cell genome, whereby the sequence is deleted utilizing a *gamete-specific* promoter, said DNA molecule comprising a recombinase site, a gamete-specific promoter operably linked to a recombinase gene, a *marker* DNA, and a recombinase site, the method comprising growing the ES cell to develop into a mouse, such that that when the gamete-specific promoter is active during gametogenesis, the recombinase gene is expressed in the mouse and the marker gene is deleted in the resulting gametes, and transgenic mice comprising a nucleic acid sequence comprising in sequential order: a recombinase site, a gamete-specific promoter operably linked to a recombinase gene, a *marker* DNA, and a recombinase site, wherein the DNA molecule has been

stably integrated into the genome of the transgenic mouse. The specification does not reasonably provide enablement for the breadth of the claims encompassing methods for deleting nucleic acid sequences from a DNA molecule that has been introduced into a mouse cell genome, whereby said sequence is deleted in a regulatable manner utilizing a promoter, said DNA molecule comprising in sequential order: a recombinase site, a promoter operably linked to a recombinase gene, a nucleic acid sequence, a recombinase site, the method comprising growing said cell such that the promoter is active, said recombinase gene is expressed in the cell and said nucleic acid sequence is deleted and transgenic mice comprising the DNA molecule. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicants argue the following: that the claims now pending relate to a nucleic acid molecule that removes foreign DNA, and a method for accomplishing this. This removal is not dependent on expression or functional expression of the foreign DNA or its removal to cure disease, and thus, not directed to gene therapy. See p. 6, 2nd ¶ of the Response. Applicants' arguments with regard to gene therapy, are found to be partially persuasive because the claims are directed to deleting a nucleic acid sequence from a mouse cell genome and do not encompass human gene therapy. Applicants argue that, with regard to the nucleic acid encoding a wild-type allele, the methods are enabled because they do not require or involve expression of

and deletion of a gene in a whole organism. Thus, the DNA molecule may be expressed in the organism, yet be deleted in a specific tissue, and that these two concepts are not mutually exclusive. For example, a gene is expressed in all other tissues and thus would be expressed in the organism but not in all the tissues of that organism. See pp. 8-9 of the Response.

This argument is not persuasive. The specification contemplates that a wild-type allele may be used in gene therapy (see p. 4, line 18). There is no clear guidance provided by the specification how this would be enabled. The Examiner agrees that the concept of deletion of a specific gene in a specific tissue is not mutually exclusive from the specific gene in the whole organism. However, the claims, as broadly written, do not enable this. The claims are directed to using vectors with any promoter. Thus, this encompasses tissue-specific promoters, but is certainly not limited to them. The specification provides no guidance as to how to 1) successfully delete a wild-type allele or fragment thereof utilizing the claimed vectors and any promoter and 2) how the deletion of the wild-type allele would occur, since it appears that the allele would be deleted upon the expression of Cre. The specification only provides guidance with regard to utilizing a marker gene and deleting the gene upon the expression of Cre. This would not be possible with any promoter, as broadly claimed.

Applicants argue that the instant invention is enabled because the method would work using any promoter, as broadly claimed, and not just a testes-specific

promoter, as taught by the specification, and further, that one of ordinary skill in the art would be aware of numerous tissue-specific promoters. Thus, because there are numerous tissue-specific promoters available in the art, Applicants argue that the law does not require numerous constructs in order to enable the instant method, and that one of skill in the art could perform the method without undue experimentation. See pp. 6-7, bridging ¶, and p. 10, 2nd ¶.

This is not persuasive. Simply noting that many tissue-specific promoters exist in the art do not provide operability to those promoters in the claimed methods. That is, the specification fails to provide guidance as to which promoters would work in the claimed methods. Furthermore, it is noted that not any promoter would work in the claimed invention. The claims as amended, broadly claim any promoter. However, it is noted that in order for the claimed invention to work, the promoter must be only active after birth, for example, or a transgenic animal would not arise, further, that a tissue-specific promoter must be used in order to specifically excise a specific nucleic acid in a specific tissue, as contemplated by the specification. The only guidance provided by the specification is with regard to gamete-specific promoters, for the generation of transgenic animals.

Applicants' arguments, with regard to the type of cell in which the method may be applied, is found to be persuasive, and that the claimed methods do not require mouse ES cells, but that mouse cells (including ES and somatic) are sufficient to enable the claimed methods. See p. 7-8 of the Response.

Applicants argue that the foreign DNA to be removed does not need to be a marker gene, because the excision of the gene is self-excision, and that if the artisan wishes to detect cells that contain the excision cassette, it would be easily achieved without resort to expression and detection of a marker gene product. Applicants argue that one of ordinary skill could use appropriate probes using methods known in the art and commonly preferred. Applicants argue that because the promoter controlling the operation is tissue-specific, excision will occur in that tissue specifically, and there is no need whatsoever to detect expression of the foreign DNA or even to express it at all in order to excise it. Thus, Applicants submit that it is a perceived failure to enable expression and detection of a marker gene is not relevant to the claimed invention when excising a non-marker gene because selection is not part of the method. See pp. 9-10 of the Response.

This is not persuasive. Firstly, it is noted that the independent claims are not limited to a tissue-specific promoter, as stated by Applicants, thus it is not clear that excision would be tissue-specific. Secondly, there is no guidance or teaching provided by the specification as to how to delete undesired DNA other than a marker gene. This is because it is unclear how, for example, a wild-type allele would be deleted in the claimed methods. The specification provides sufficient guidance with regard to utilizing the claimed vectors in methods to delete marker genes. Although it may be possible to use appropriate probes to detect a gene, the specification has not enabled these other genes. The specification clearly

contemplates excising wild-type alleles in applications such as gene therapy, but fails to provide guidance as to how to accomplish this excision. As stated previously, it is unclear, how, with any promoter (as broadly claimed) one would specifically excise a wild-type allele in a specific tissue.

Accordingly, in view of the lack of teaching or guidance with regard to utilizing any promoter for self-excision, other than a gamete-specific promoter, and utilizing any foreign DNA, other than a marker sequence, to produce transgenic mice, it would have required undue experimentation for one of skill in the art to make and use the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 20-24, 32, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 20, as amended, is unclear. The claim, as amended, recites "removing a nucleic acid sequence" which encompasses the entire nucleic acid molecule as claimed (including the recombinase site, the promoter, the recombinase gene, the nucleic acid sequence, and the second recombinase site). Further, it encompasses nucleic acid sequences that have been inserted into other parts of the mouse

genome because it is unclear that the nucleic acid sequence to be removed is the same as the one in part (d) of the claim. Appropriate correction is required. Claims 21-24 and 32 depend from claim 20.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The prior rejection of claims 20-24, 32 and 43-45 under 35 U.S.C. 102(b) as being anticipated by Russ *et al.* [J. Virol., 70(8):4927-4932 (1996)] is maintained for reasons of record.

The claims are directed to a nucleic acid molecule for removing a nucleic acid sequence that has been inserted into a host cell, the molecule comprising in sequential order (a) a recombinase site, (b) a promoter operably linked to (c) a recombinase gene (d) the nucleic acid and (e) a recombinase site. In further embodiments, the recombinase site can be loxP or FRT and the recombinase gene can be Cre or FLP.

Applicants that Russ do not teach the nucleic acid molecule as instantly claimed because they do not teach a recombinase site, a promoter linked to a

recombinase gene, the nucleic acid to be excised, and a second recombinase site. See p. 11-12 of the Response.

This is not persuasive. In figure 4A, Russ teach the claimed nucleic acid molecule because there is additional nucleic acid sequences following Cre. Thus, they do teach the claimed invention because they show a lox site, a promoter, a recombinase gene, a nucleic acid sequence, and a recombinase site.

Russ teach the generation of a retroviral vector having duplication of terminal control regions U5 and U3 to generate LTRs, utilizing Cre positioned between two loxP target sequences to exise most of the viral and nonviral sequences unrelated to the transcription of the U3 gene. See *Abstract.* Russ teach the southern blot analysis of NIH 3T3 cells expressing the U3pgklxtkneoMCCre proviruses. See Figure 3. Russ further teach that the vectors pggSVCreU3lxpgkpuro and pggSVCreU3lxSVpuro were used to transfect BOSC23 cells to obtain an infectious virus, and the titers of the recovered viruses were determined on NIH3T3 cells by selection of puromycin. They teach that genomic DNA of the puromycin-resistant colonies were analyzed and it was found that in 12 of 14 recombined clones, the sequences flanked by *loxP* were absent, indicating the recombination of the proviruses. See figure 4, and particularly 4A.

Accordingly, Russ anticipate the claimed invention.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Amy Nelson, Acting SPE of Art Unit 1632, at (571) 272-0804. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

tnt
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